PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
ZRC-MC-021		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IN2005/000011	07.01.2005	09.01.2004

International Patent Classification (IPC) or national classification and IPC

INV. C07D405/06 C07D319/06 C07D413/06 C07D495/04 C07D417/06 C07D407/06 A61K31/357 A61P3/04 C07D405/12

Applicant

CADILA HEALTHCARE LIMITED

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      - ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.07.2005	04.05.2006

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IN2005/000011

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-34	as originally filed

Claims, Numbers

2(part), 3-11	as originally filed
1, 2(part)	received on 26.09.2005 with letter of 23.09.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5(part),7-10

because:

☒ the said international application, or the said claims Nos. 7-10 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 5(part) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☒ no international search report has been established for the said claims Nos. 5(part)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5
	No:	Claims	1-4,6-11
Inventive step (IS)	Yes:	Claims	5
	No:	Claims	1-4,6-11
Industrial applicability (IA)	Yes:	Claims	1-6,11
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

I. Basis of the report

The amendments filed with the letter dated 23.9.05 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. In the original disclosure proviso i) excluded compounds wherein X is CH_2, A is a substituted heterocyclic group wherein the substituent is aryl, aromatic, heterocyclic or cycloalkyl. However, these compounds are no longer excluded. Therefore the presently amended claim 1 extends to compounds which were not part of the original disclosure. In addition, the amended proviso i) amounts to a newly introduced proviso, as its content is different from that in the original disclosure. The European Patent Office allows disclaimers without basis in the original application to be introduced only to exclude subject matter from a disclosure which is considered to be an "accidental anticipation". A disclosure is considered to be an accidental anticipation if it is so unrelated to and remote from the claimed invention that the person skilled in the art would never have taken it into consideration when making the invention. However, the amended proviso has been introduced to exclude compounds of D1. This document is considered to be highly relevant for the assessment of inventive step as it concerns compounds with the same activity. Thus a disclaimer newly introduced to exclude compounds of D1 is not allowable. As the amendments are not allowable the following examination has been performed for the claims in their original form.

III. Non-establishment of opinion

Claims 7-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

There are 2 claims numbered "3" and no claim 5. The following examination has been based on the claims wherein the 2nd claim presently numbered "3" is treated as claim 4 and present claim 4 is renumbered as claim 5.

A number of examples (3, 12, 17, 26, 35, 37, 48) do not fall within the scope of formula (I) of present claim 1. These examples are claimed in claim 5 as being compounds of claims 1-3. This introduces a contradiction into the claims, which

creates a lack of clarity (Article 6 PCT) concerning the scope of the claims. Only formula (I) has been searched, thus no opinion will be established for those compounds of claim 5 not falling within this formula.

V. Reasoned statement

Reference is made to the following documents:
D1: EP-A-1 295 875
D2: Albany Molecular Research, Inc. Technical Reports, vol. 7, no. 46, 2002, p. 8-9
D3: WO00/04011

Novelty

In claim 1 compounds wherein A is i.a. optionally substituted heteroaryl or optionally substituted heterocyclyl are claimed. Thus it is clear that the term "heterocyclyl" does not include heteroaryl - if it did, both possibilities would not be separately listed in the claim. In proviso i) compounds wherein A is heterocyclyl having aryl, aromatic, heterocyclic or cycloalkyl substituents are excluded. No mention is made of an exclusion of compounds wherein A is heteroaryl having these substituents. D1 discloses a general formula [1] wherein the group corresponding to the present A is a divalent aromatic heterocyclic group, i.e. a heteroaryl group. This disclosure overlaps with the present claims. The compounds are described as being effective at lowering triglyceride, LDL-C and insulin levels in the blood and can thus be useful in the treatment of i.a. diabetes and obesity. Furthermore, D1 discloses specific compounds falling within the scope of the present claims (e.g. the compounds of examples 1-4). D2 elaborates on the mechanism of action of one of the compounds of D1, stating that it is a selective PPAR-alpha activator.
These disclosures are novelty-destroying for present claims 1-4 and 6-11.
D3 discloses general formula I wherein R^2 or R^3 may be $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_7)$alkyl wherein the aryl group may optionally be substituted. In present claim 1, proviso ii) excludes certain compounds wherein A is a substituted aryl group, however there is no exclusion of compounds wherein A is an unsubstituted aryl group. The compounds of D3 are described as being activators of PPAR-alpha and gamma, useful as hypolipidemic and hpyoglycemic agents. Thus the disclosure of D3 overlaps with present claims 1, 3 and 7-10.

Claims 1-4 and 6-11 do not fulfil the requirements of Article 33(2) PCT.

Inventive step

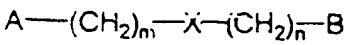
In view of their lack of novelty, claims 1-4 and 6-11 cannot be inventive.
Re. those compounds of claim 5 which fall within the scope of formula (I):
For those compounds wherein A is heterocyclic or heteroaryl, D1 is taken as the closest prior art. The compounds of D1 all have 2 rings directly attached to one another (R^1-Het-). None of the compounds of claim 5 have this feature. It does not appear obvious to provide further compounds with PPAR modulating activity by replacing the R^1 ring of D1 by one of the substituents given in claim 5. Thus for the compounds wherein A is heterocyclic or heteroaryl, claim 5 may be considered inventive.
For the compounds wherein A is aryl, D3 may be taken as the closest prior art. The compounds of claim 5 differ in the identity of the substituent on the aryl group. The structurally closest compounds are ex. 18 and 19, which possess a phenyl ring substituted by a benzyloxy group and a methanesulfonyloxy group, whereas the compounds of D3 may have an aryl group substituted by a hydroxy group, a trifluoromethoxy group or alkoxy group. In the absence of any teaching that the substituents of present claim 5 and those of D3 are equivalent in compounds with PPAR modulating activity, it does not appear to be obvious to provide further compounds with this activity by modifiying the compounds of D3 in the way claimed. Thus the compounds of claim 5 which fall within the scope of claim 1 and which have the alleged activity may be considered inventive.
Claims 1-4 and 6-11 do not fulfil the requirements of Article 33(3) PCT.
Claim 5 fulfils the requirements of Article 33(3) PCT.

Industrial applicability

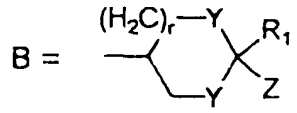
Claims 1-6 and 11 fulfil the requirements of Article 33(4) PCT.
No unified criteria exist in the PCT Contracting States for assessing whether present claims 7-10 are industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

We claim:

A compound of formula (I):



(I)



their tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, pharmaceutical compositions containing them, wherein 'A' represents optionally substituted, single or fused aryl, cycloalkyl group or an optionally substituted heteroaryl or an optionally substituted heterocyclyl group; 'm' = 0-2; 'n' = 3-6; 'X' represents O, S, -N-(Ra)- or $-CH_2-$; Ra represents H, linear or branched, group selected from alkyl, acyl or aryl, aralkyl group, which may optionally be substituted; 'Y' at each occurrence independently represent O or S; R_1 represents H, linear or branched substituted or unsubstituted alkyl; r = 0-2; Z represents $-(CH_2)_sCOOH$, alkoxycarbonyl, hydroxymethyl, -CN, substituted or unsubstituted tetrazoles, alkylcarbonyl groups, s = 0-4; with the proviso that when 'X' = CH_2 and

i) 'A' represents substituted aromatic heterocyclic group, the substitutions on 'A' does not represent aryl, aromatic, heterocyclic or cycloalkyl group; and

ii) 'A' represents substituted aryl group, the substituent on 'A' represents alkylsulfonyloxy, aryloxy, aralkoxy, cycloalkyl, heteroaryl or heterocyclic group.

2. A compound as claimed in claim 1 wherein, when 'A' is substituted, suitable substitutions on 'A' may be selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyi, aikoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, alkylsulfonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino,